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Expert Medical Witness Report

Ferrell vs. The United States of America
Case #16-CV-192

A. Witness qualifications and publications for the last 10 years

I am an Investigator-track Assistant Professor in the Department of Pediatrics, Division of Pediatric Rheumatology at Washington University School of Medicine. I attended The Ohio State University from 1996-2004, earning a Ph.D. in the field of Immunology and a medical degree (M.D.), graduating with honors. The focus of my PhD work was basic immunologic mechanisms of cellular activation. Following medical school I attended residency and fellowship in Pediatrics and Pediatric Rheumatology and Immunology at Washington University/St. Louis Children's Hospital (2004-2010). I have been a faculty member in the Department of Pediatrics at Washington University since 2010, and am board certified in Pediatrics and Pediatric Rheumatology. I currently direct an Immunology research laboratory at Washington University, care for patients in Pediatric Rheumatology and Immunology outpatient clinics, and serve as inpatient attending for the Pediatric Rheumatology and Immunology services ~4 weeks per year. The focus of my research is on mechanisms by which immune cells in our body become activated, and genetic causes of primary immunodeficiency diseases. I have published more than 40 journal articles, reviews, and chapters in the field of basic and clinical Immunology and Rheumatology (see CV) including a rare report of a young patient with vancomycin-induced drug reaction with eosinophilia and systemic symptoms (DRESS), highlighted in bold below.

Publications from 2007-2017

1. **Cooper MA**, Willingham DL, Brown DE, French AR, Shih FF, White AJ. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. *Arthritis Rheum*. 2007;56(9):3107-11. PMID:17763414

2. **Cooper MA**, Elliott JM, Keyel PA, Yang L, Carrero JA, Yokoyama WM. Cytokine-induced memory-like natural killer cells. *Proc Natl Acad Sci U S A*. 2009;106(6):1915-9. PMID:19181844
3. **Cooper MA**, Colonna M, Yokoyama WM. Hidden talents of natural killers: NK cells in innate and adaptive immunity. *EMBO Rep*. 2009;10(10):1103-10. PMID: 19730434
4. **Cooper MA**, Yokoyama WM. Memory-like responses of natural killer cells. *Immunol Rev*. 2010;235(1):297-305. PMID: 20536571
5. **Kitcharoensakkul M, Ree N, Bloomberg GR, Dehner LP, Heidingsfelder JA, White AJ, Cooper MA. Vancomycin-induced DRESS with evidence of T-cell activation in a 22-month-old patient. *Ann Allergy Asthma Immunol*. 2012;109(4):280-1. PMID:23010236**
6. Romee R, Schneider SE, Leong JW, Chase JM, Keppel CR, Sullivan RP, **Cooper MA**, Fehniger TA. Cytokine activation induces human memory-like NK cells. *Blood*. 2012;120(24):4751-60. PMID:22983442
7. Keppel MP, Yang L, **Cooper MA**. Murine NK cell intrinsic cytokine-induced memory-like responses are maintained following homeostatic proliferation. *J Immunol*. 2013;190(9):4754-62. PMID:23530145
8. Lim E, Tao Y, White AJ, French AR, **Cooper MA**. Hypogammaglobulinemia in pediatric systemic lupus erythematosus. *Lupus*. 2013;22(13):1382-7. PMID:24106215
9. Deady LE, Todd EM, Davis CG, Zhou JY, Topcagic N, Edelson BT, Ferkol TW, **Cooper MA**, Muenzer JT, Morley SC. L-plastin is essential for alveolar macrophage production and control of pulmonary pneumococcal infection. *Infect Immun*. 2014. PMID:24595139
10. Leong JW, Chase JM, Romee R, Schneider SE, Sullivan RP, **Cooper MA**, Fehniger TA. Preactivation with IL-12, IL-15, and IL-18 induces CD25 and a functional high-affinity IL-2 receptor on human cytokine-induced memory-like natural killer cells. *Biol Blood Marrow Transplant*. 2014;20(4):463-73. PMID:24434782
11. Tarbox JA, Keppel MP, Topcagic N, Mackin C, Ben Abdallah M, Baszis KW, White AJ, French AR, **Cooper MA**. Elevated double negative T cells in pediatric autoimmunity. *J Clin Immunol*. 2014;34(5):594-9. PMID:24760111
12. Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pedersen A, Niemela JE, Lyons JJ, Engelhardt KR, Zhang Y, Topcagic N, Roberson ED, Matthews H, Verbsky JW, Dasu T, Vargas-Hernandez A, Varghese N, McClain KL, Karam LB, Nahmod K, Makedonas G, Mace EM, Sorte HS, Perminow G, Rao VK, O'Connell MP, Price S, Su HC, Butrick M, McElwee J, Hughes JD, Willet J, Swan D, Xu Y, Santibanez-Koref M, Slowik V, Dinwiddie DL, Ciaccio CE, Saunders CJ, Septer S, Kingsmore SF, White AJ, Cant AJ, Hambleton S, **Cooper MA**. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. *Blood*. 2015;125(4):591-599. PMID:25359994
13. Vogel TP, Milner JD, **Cooper MA**. The Ying and Yang of STAT3 in Human Disease. *J Clin Immunol*. 2015. PMID: 26280891
14. Keppel MP, Saucier N, Mah AY, Vogel TP, **Cooper MA**. Activation-specific metabolic requirements for NK Cell IFN-γ production. *J Immunol*. 2015;194(4):1954-1962. PMID:25595780
15. **Cooper MA** and White AJ. Pediatric Rheumatology. In: White AJ, eds. *Washington Manual of Pediatrics* 2016:Ch. 23 (most recent chapter).
16. Fotis L, Baszis KW, French AR, **Cooper MA**, White AJ. Mesenteric vasculitis in children with systemic lupus erythematosus. *Clin Rheumatol*. 2016;35(3):785-93. PMID:25687984
17. Romee R, Rosario M, Berrien-Elliott MM, Wagner JA, Jewell BA, Schappe T, Leong JW, Abdel-Latif S, Schneider SE, Willey S, Neal CC, Yu L, Oh ST, Lee YS, Mulder A, Claas F, **Cooper MA**, Fehniger TA. Cytokine-induced memory-like natural killer cells exhibit

enhanced responses against myeloid leukemia. *Sci Transl Med.* 2016;8(357):357ra123. PMID:27655849

18. Walter JE, Farmer JR, Foldvari Z, Torgerson TR, **Cooper MA.** Mechanism-Based Strategies for the Management of Autoimmunity and Immune Dysregulation in Primary Immunodeficiencies. *J Allergy Clin Immunol Pract.* 2016;4(6):1089-1100. PMID: 27836058
19. Keppel MP, **Cooper MA.** Assessment of NK Cell Metabolism. *Methods Mol Biol.* 2016;1441:27-42. PMID: 27177654
20. Mah AY, **Cooper MA.** Metabolic Regulation of Natural Killer Cell IFN-γ Production. *Crit Rev Immunol.* 2016;36(2):131-147. PMID: 27910764
21. **Cooper MA.** Teach Your NK Cells Well. *Immunity.* 2016;45(2):229-31. PMID: 27533007
22. Fehniger TA, **Cooper MA.** Harnessing NK Cell Memory for Cancer Immunotherapy. *Trends Immunol.* 2016. PMID: 27773685

B. Case history including facts and data considered

This is the case of Jordan Dixon, born June 19, 1999, who died on 12/21/2014 from myocarditis, DRESS syndrome, RSV, rhinovirus/enterovirus according to the death certificate filed on Dec. 26, 2014. The opinions below are based on history was obtained from medical records provided by the US Attorney's office and witness depositions. The facts below are related to the initial diagnosis of DRESS in this patient.

Jordan was a 15 year-old African-American male was admitted to Cardinal Glennon Hospital (CGH) on July 11, 2014 with a rash, fever, and fatigue. Prior visits to medical providers included:

1. June 2, 2014: Well-child exam, Dr. Quass, primary pediatrician. At this exam, Jordan was noted to have acne refractory to topical therapy and was prescribed minocycline, 100 mg twice daily.
2. July 1, 2014: Urgent Care visit, Dr. Middendorf. At this visit, Jordan was diagnosed with pharyngitis and acute bronchitis. Clinic notes indicate that he had a 3d history of a sore throat, cough, vomiting, rash, swollen lymph nodes, and subjective fever. He was febrile at this visit, a chest x-ray was interpreted as normal, and rapid tests for Group A strep and EBV mononucleosis were negative. Laboratory studies demonstrated elevated creatinine (1.0) with normal BUN (8), low white blood cell count (4.2), and low platelet count (122). He was diagnosed with a viral syndrome, acute bronchitis, and viral rash and was prescribed azithromycin for 5 days.
3. July 3, 2014: Dr. Quass, primary pediatrician. Jordan presented with fever, cough, and pruritic rash. Jordan was referred to Cardinal Glennon Children's Hospital for further evaluation, including concern for possible measles infection.

4. July 3, 2014: Cardinal Glennon Emergency Department. At this visit notes indicate that Jordan had a 1 week history of fever, productive cough, congestion, rhinorrhea, vomiting, diarrhea, and a rash that started after taking azithromycin. He was reported to be taking griseofulvin for a scalp rash. There was no mention of minocycline as a current medication in this medical record. Laboratory studies were significant for negative rapid Group A strep and EBV mononucleosis tests, and negative antibody testing for measles. He had several laboratory abnormalities including transaminases elevated >2 times the normal limit (AST and ALT) and bilirubin, concerning for liver disease; elevated BUN and creatinine (~50% above normal), concerning for kidney disease; and mild hyponatremia (low sodium), consistent with dehydration with vomiting/diarrhea. Thus, laboratory studies at this visit demonstrated liver and kidney abnormalities. There was mention of a possible drug reaction in the medical record; however the final diagnosis was listed as "Infectious Mononucleosis". Jordan was discharged with instructions to stop azithromycin, and prescribed an antihistamine medication (hydroxyzine) and topical steroids for his rash.
5. July 8, 2014: Dr. Quass, primary pediatrician. Jordan presented with rash, joint swelling, fatigue, and fever. On physical exam he had hepatosplenomegaly and lymphadenopathy. Laboratory studies were ordered and he was prescribed prednisone and subsequently referred to an infectious disease specialist at CGH. Laboratory studies from this visit were significant for an elevated white blood cell count, with a differential reported on 7/11/14 that showed significant eosinophilia.

On admission to CGH on 7/11/14, prednisone was stopped and laboratory studies were significant for an elevated white blood cell count with eosinophilia (25%) and elevated transaminases. Admission notes from his July 11th hospitalization indicate that his symptoms started 3 weeks prior (~June 20th) during marching band practice. Notes from a 7/12/14 consultation states that Jordan had been practicing outside, marching 2.5 miles daily Mon-Fri between the hours of 1-5PM. It was reported that after a marching band practice he felt nauseated and dizzy, received fluids to drink, but had continued symptoms and developed a rash the next day.

On approximately 7/12/14 Jordan was diagnosed with DRESS syndrome thought to be secondary to 6 weeks of minocycline usage based on the history provided. He was started on IV steroids on 7/13/14, two days after admission. His eosinophilia completely resolved by

7/15/14 (0% eosinophils). He also had rhabdomyolysis, with an elevated CK level (1871 U/L) first measured on 7/13/14. His CK level continued to be elevated >1000 U/L until 7/20/14. He also had evidence of nephritis with blood and protein in his urine. Infectious disease testing was positive for HHV-6 re-activation. There was concern for possible myocarditis, and an echocardiogram was interpreted as demonstrating hyperdynamic biventricular systolic function and he was not felt to have myocarditis. He received supportive care, steroids, IVIG, and showed improvement. His steroids were eventually decreased and he was discharged home on 7/23/14 with normal white blood cell and eosinophil counts, elevated but improved CK (528 U/L), elevated transaminases, and normal markers of renal function (BUN/Cr and urinalysis). Jordan was discharged home with a prednisone taper and amlodipine (a hypertension medication) with scheduled follow-up.

He was subsequently re-admitted to CGH on 8/13/14 with fevers, weight loss, weakness, rash, hypotension, and tachycardia. He had a prolonged hospital stay with discharge on 11/13/14. Blood cultures drawn in the emergency department at the time of admission were positive for Staphylococcal aureus. Upon admission he required supportive care in the PICU with evidence of cardiac dysfunction on echocardiogram and received antibiotics and high dose steroids. A cardiac MRI on 8/21/14 was normal and the etiology of his cardiac dysfunction was felt to be DRESS syndrome versus hypoperfusion associated with sepsis. During his hospitalization he was started on steroid sparing agents including cyclosporine, then Neoral, followed by azathioprine. On 10/2/14 he again grew Staphylococcal aureus from his blood, this time resistant to methicillin (MRSA) and associated with endocarditis (infection of the valves of the heart). A later brain MRI showed frontal lobe infarcts felt to be due to MRSA bacteremia. Additional imaging of his bones was concerning for osteomyelitis by report. He developed worsening cardiac function and steroid-induced hyperglycemia requiring insulin. He was discharged on multiple medications including prednisone, cyclosporine, linezolid, Lasix, Diurel, insulin, digoxin, and atenolol. His discharge diagnoses included: MRSA endocarditis, myocarditis associated with DRESS syndrome, steroid-induced hyperglycemia, cerebral septic emboli, congestive heart failure, anemia, and rash.

Jordan was re-admitted to the hospital on 11/22/14 with fever and fatigue. He received supportive care in the PICU for cardiac dysfunction/congestive heart failure. During this hospital stay his cyclosporine was discontinued and his steroids were weaned down. He was discharged to home on 12/15/14. He returned to the hospital on 12/20/14 with cardiac failure and subsequently died on 12/21/14.

Additional information from witness deposition and US Attorney's evidence

Evidence demonstrates that on 6/2/14 Dr. Quass prescribed 60 tablets of minocycline, 100mg to be taken twice daily. This prescription was filled once, and that pill bottle provided by Jordan's mother contained 39 tablets of minocycline, suggesting that Jordan may have taken as many as 21 tablets of minocycline between 6/4/14 and an unknown period.

Summary of Case

In summary, Jordan Dixon was a 15 year-old male who developed rash, eosinophilia, rhabdomyolysis, liver dysfunction, and nephritis suspected to be caused by DRESS syndrome associated with minocycline use. He did well following his initial hospitalization on 7/11/14, but subsequently developed sepsis, MRSA endocarditis, cardiac dysfunction, and expired on Dec. 21, 2014 due to heart failure. With regards to the timeframe from his initial presentation to Dr. Quass' office on 7/3/14 and his hospitalization at CGH on 7/11/14, the following facts are particularly relevant to the summary opinion below: 1) the timeframe of when minocycline was taken is unknown based on the finding that only 21 of 60 tablets from the initial prescription were gone from the bottle, and 2) Jordan had evidence of liver and kidney dysfunction at his 7/3/14 visit to CGH emergency department.

C. DRESS syndrome

DRESS syndrome is a rare drug-induced reaction that affects less than 1 in 100,000 individuals, characterized by systemic symptoms such as fever and fatigue associated with eosinophilia, rash, and organ system involvement, predominantly liver and kidney. The drugs that most commonly cause DRESS syndrome are anti-seizure medications and allopurinol, a medication most often used to treat gout. Diagnosis of DRESS syndrome can be challenging, and other disorders mimic DRESS syndrome, including infections and autoimmune disorders. Because of the challenges in diagnosing DRESS, a diagnostic validation scoring system was recently proposed by the RegiSCAR Project, a European registry of severe drug reaction. This scoring system includes points for lymphadenopathy, eosinophilia, atypical lymphocytes, and skin rash. It is also recommended that if there is organ system involvement, that other potential causes of disease, including hepatitis A, B, and C, HIV, chlamydia, mycoplasma, sepsis (positive blood culture), and autoimmune disease be excluded as potential causes.

The pathogenesis of DRESS syndrome is unknown, but thought to involve hyper-activation of the immune response triggered by a drug. Several studies have demonstrated hyper-activation of T lymphocytes, which may contribute to the pathogenesis of DRESS. Re-activation of viral infections including Epstein Barr Virus (EBV) and human herpesvirus 6 and 7 (HHV6 & HHV7) have been reported in the majority of patients with DRESS syndrome (~50-80%), but it is unknown whether these viral infections are involved in the pathogenesis of DRESS or the result of immune activation during DRESS. Treatment for DRESS consists of removal of the offending drug, supportive care, and immunosuppressive therapy with corticosteroids and other agents if required. While most patients respond to therapy for DRESS, mortality from DRESS has been reported to be between 2 and 10% and is most often associated with liver disease.

In the largest prospective study of adult patient with DRESS syndrome (Kardaun et al, Br J Dermatol, 2013), 117 cases from a multiple countries, a causative drug was identified in 88% of the cases, with the majority being anti-seizure medications followed by allopurinol, sulfonamide antibiotics, and then other antibiotics (11%). Minocycline was associated with 4 of the 117 cases, with a median latency of 20 days from start of drug to the onset of symptoms, and an interquartile range of 17-26 days. Similar studies in pediatric patients are lacking and limited to case reports due to the rarity of this disease. The authors of this study note that DRESS is challenging to diagnosis and requires exclusion of other causes, the variability of presentation frequently results in delayed diagnosis, and that not all physicians are familiar with DRESS.

D. Diagnosis of DRESS syndrome in this case

Based on review of the available medical records, it is my medical opinion that this patient likely had DRESS syndrome at his initial hospitalization on 7/11/14. This patient's DRESS syndrome showed rapid improvement with corticosteroid therapy as evidenced by the absence of eosinophilia and atypical lymphocytes by the time of discharge. Based on evidence demonstrating that this patient was not compliant with minocycline therapy, and thus the high likelihood that he did not take minocycline for two weeks prior to onset of symptoms, the drug that caused DRESS syndrome in this case is not clear. There are several unusual aspects of this case:

1. The timeframe of minocycline usage is unclear, based on the finding that 21 pills were taken during an unspecified timeframe. If these tablets had been taken as prescribed (twice daily), this would be equivalent to 10.5 days of medication. This finding conflicts with notes from his 7/11/14 hospitalization, where a history was obtained that he had taken minocycline for 6 weeks, more consistent with a time period that could trigger

DRESS. There are no clear diagnostic guidelines for time of exposure to a drug before the onset of DRESS syndrome, but expert opinion states that drugs taken for <2 weeks or >3 months are unlikely to be the causative agent of DRESS syndrome (Roujeau, Up To Date, October 2016). The medical records indicate that this patient was also taking griseofulvin (at his 7/3/14 ED visit), for an unknown length of time. This drug has also been associated with DRESS syndrome in a child (Smith et al, Pediatric Dermatology, 2016) and is a well-described cause of liver damage.

2. The patient had clear evidence of liver and kidney dysfunction at his ED visit on 7/3/14. His transaminases were greater than 2-fold increased over normal limits, a level that experts agree warrants further evaluation for causes of hepatitis (Friedman, UpToDate, 2016). Other causes of hepatic dysfunction including hepatitis A, B, and C and viruses causing rash and myocarditis (including CMV, parvovirus, and coxsackie group B) were not evaluated, and could have contributed to the organ system involvement in this case. He was reported to be taking griseofulvin at this ED visit, which is known to be associated with liver toxicity, however there was no mention in the medical record of any recommendation to stop this medication. Hemophagocytic lymphohistiocytosis (HLH) would be another rare cause of liver disease, and is also associated with rash and lymphadenopathy. His laboratory studies also demonstrated a significantly elevated creatinine greater than 50% above normal, concerning for kidney disease. No further liver or kidney function testing, such as coagulation studies (liver) or urinalysis (kidney) were performed at this ED visit. Thus, there is evidence of end-organ damage on 7/3/14, but the extent of organ dysfunction and specific causes were not investigated. The presence of organ damage on 7/3/14 placed Jordan at increased risk for morbidity and mortality related to DRESS, since organ damage, including liver damage, is the greatest predictor of death from DRESS.
3. This patient presented with rhabdomyolysis (muscle inflammation), which may have contributed to his kidney disease. Rhabdomyolysis has very rarely been reported in DRESS. A literature review revealed only one published case of minocycline-induced DRESS associated with rhabdomyolysis: a dancer in whom the authors speculated vigorous activity contributed to the rhabdomyolysis and complicated the diagnosis (Rahman et al, Int J Dermatol, 2002). A separate report described a child chronically treated with bipolar medications, who developed DRESS syndrome in response to these medications due to rhabdomyolysis caused by acute caffeine ingestion. It was felt that the rhabdomyolysis caused impaired kidney function and altered drug metabolism,

contributing to the development of DRESS syndrome (Mahaptra et al, Pediatrics, 2011). In the current case, the medical records indicate that the patient's symptoms started immediately after a vigorous band practice when he was dehydrated. Marked exertion with hyperthermia is a well-established cause of rhabdomyolysis, and this patient had evidence of kidney dysfunction on 7/1/14 with an elevated creatinine. Therefore, it is possible that exercise-induced rhabdomyolysis contributed to the development of DRESS syndrome in this case.

4. This patient was admitted to the hospital on 8/13/14 from a presumed recurrence of DRESS syndrome; however his symptoms were actually due to septic shock. Prior to recognition of septic shock, he was treated in the hospital with high dose of steroid for presumed recurrence of DRESS syndrome. This episode of septic shock led to a prolonged hospitalization, including prolonged treatment in the intensive care unit to maintain his cardiac function. Subsequently, on 10/1/14, he developed an infection of his heart (endocarditis), with vegetations on the mitral valve due to methicillin-resistant Staphylococcal aureus (MRSA). This infection led to infarcts in his brain, which according to medical records were likely secondary to disseminated MRSA infection. Based on blood cultures, he had continued systemic infection with MRSA from 10/1/14 until 10/17/14, when he had his first negative blood culture after diagnosis. Overall, Jordan's clinical course and complications following his hospitalization on 8/13/14 appear to have been primarily associated with complications from infections which by themselves have a higher rate of mortality than DRESS syndrome. The estimated mortality rate from sepsis in children associated with endocarditis, central nervous system infection, and bacteremia (infection in the bloodstream), all of which this patient had, is estimated to be 15 to 20%, and even higher for MRSA (Weiss and Pomerantz, UpToDate, 2017). Prior to this hospitalization, he did not have evidence of DRESS-associated myocarditis according to the medical records. A cardiac MRI on 8/20/14 to evaluate for DRESS-associated myocarditis was interpreted by the cardiologists as normal, and did not support DRESS-induced myocarditis. A cardiac biopsy to evaluate for DRESS-induced myocarditis was not performed, thus there was no direct evidence that his cardiac dysfunction was due to DRESS. An autopsy was not performed in this case.

E. Conclusions and statement of expert medical opinion

1. Diagnosis: It is my medical opinion that Jordan Dixon more than likely had DRESS syndrome at the time of his 7/11/14 hospitalization. In my opinion, the causative agent of his DRESS syndrome in this case is unclear, due to the unknown duration of exposure to minocycline or other drugs known to cause DRESS (including griseofulvin) prior to development of symptoms. DRESS is a very rare drug hypersensitivity reaction, whose symptoms closely resemble a viral infection including prominent fever, fatigue, rash, and lymphadenopathy.

2. Care by Dr. Quass: It is my opinion that the primary pediatrician in this case, Dr. Quass, provided appropriate care by recognizing that the Jordan was ill-appearing and immediately referring him for further evaluation and medical expertise. The symptoms of DRESS syndrome very closely resemble infection, which is exceedingly more common than DRESS syndrome in pediatric patients. It is within the standard of care to refer a pediatric patient to the emergency department (ED) without sending medical records, and it would be uncommon practice for a pediatrician to send general medical records for an ED referral, in particular since Dr. Quass had not performed any testing that the ED needed to be aware of. It would be within the standard of care for providers in the ED to obtain a full medical history, including medication usage, from a patient and parents.

3. Outcome in this case: It is not clear from the evidence provided that Jordan's outcome would have been different if DRESS were diagnosed at his initial visit with Dr. Quass on 7/3/14 rather than at his 7/11/14 hospitalization. Jordan had clear evidence of liver and kidney dysfunction at his 7/3/14 ED visit, which were not fully investigated. Organ damage in DRESS syndrome, in particular liver damage, constitutes the highest risk for mortality. It is common for DRESS syndrome to relapse even after the offending drug is withdrawn, and prolonged courses of immune suppression are frequently required for treatment. Based on the presence of organ damage on 7/3/14, if DRESS had been diagnosed at that time, he more than likely would have required a prolonged steroid course and immune suppression to adequately treat his disease. This immune suppression would have resulted in similar risk of complications that this patient experienced and which more than likely played a significant role in his death, including sepsis and endocarditis. Jordan presented in septic shock on 8/13/14, and his course was complicated by abnormalities in his brain caused by infection and endocarditis, which together are associated with a high mortality rate.

F. References and potential exhibits that may be used to summarize or support witness testimony:

1. CV, Megan A. Cooper, MD, PhD
2. Medical records, witness deposition statements, and other documents provided to this witness by the US Attorney's office.
3. References cited and used to prepare this report:
    a. Kardaun SH et al. "Drug reaction with eosinophila and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study". British Journal of Dermatology, 2013.
    b. Cacoub P et al. "The DRESS syndrome: a literature rerview". American Journal of Medicine, 2011.
    c. Rahman Z et al. "Minocycline hypersensitivy syndrome manifesting with rhabdomyolysis". Int J Dermatol, 2002.
    d. Smith RJ et al. "Probably griseofulvin-induced drug reaction with eosinophilia and systemic symptoms in a child". Pediatric Dermatology, 2016.
    e. Mahaptra S et al. "Psychotropic drug-related eosinophilia with systemic symptoms after acute caffeine ingestion". Pediatrics, 2011.
    f. Jean-Claude Roujeau, "Drug reaction with eosinophilia and systemic symptoms (DRESS)", UpToDate, https://www.uptodate.com/contents/drug-reaction-with-eosinophilia-and-systemic-symptoms-dress. 2017.
    g. Lawrence Friedman, "Approach to the patient with abnormal liver biochemical and function tests", UpToDate, https://www.uptodate.com/contents/approach-to-the-patient-with-abnormal-liver-biochemical-and-function-tests. 2016.
    h. Scott Weiss and Wendy Pomerantz, "Septic shock: ongoing management after resuscitation in children", UpToDate, https://www.uptodate.com/contents/septic-shock-ongoing-management-after-resuscitation-in-children.

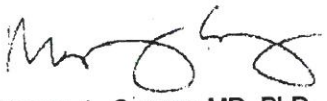
G. Other cases the witness has testified at trial or by deposition in the last 4 years:

None

H. Witness Compensation:

1. Review of case, literature, and preparation of report: $400/hr.
    a. Total hours as of 1/31/17: 20.7 hours, $8280
2. Witness testimony, deposition and/or court appearance: $500/hr.

a. Total hours as of 1/31/17: 0.



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